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PTO-1390 (Modified) U.S. DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE
(REV. 12-2000)

TRANSMITTAL LETTER TO THE UNITED STATES DESIGNATED/ELECTED OFFICE (DO/EO/US) CONCERNING A FILING UNDER 35 U.S.C. 371

ATTORNEY'S DOCKET NUMBER	
NIDN-10484	
U.S. APPLICATION NO. (IF KNOWN, SEE 37 CFR)	
To be assigned 09/830147	
INTERNATIONAL APPLICATION NO	INTERNATIONAL FILING DATE
PCT/GB99/03488	October 22, 1999
PRIORITY DATE CLAIMED	
October 22, 1998	

TITLE OF INVENTION
Eur opium Switch

APPLICANT(S) FOR DO/EO/US
Kenneth Kellar

Applicant herewith submits to the United States Designated/Elected Office (DO/EO/US) the following items and other information:

1. ☒ This is a **FIRST** submission of items concerning a filing under 35 U.S.C. 371.
2. ☐ This is a **SECOND** or **SUBSEQUENT** submission of items concerning a filing under 35 U.S.C. 371.
3. ☒ This is an express request to begin national examination procedures (35 U.S.C. 371(f)). The submission must include itens (5), (6), (9) and (24) indicated below.
4. ☒ The US has been elected by the expiration of 19 months from the priority date (Article 31).
5. ☒ A copy of the International Application as filed (35 U.S.C. 371 (c) (2))
   a. ☒ is attached hereto (required only if not communicated by the International Bureau).
   b. ☒ has been communicated by the International Bureau.
   c. ☐ is not required, as the application was filed in the United States Receiving Office (RO/US).
6. ☐ An English language translation of the International Application as filed (35 U.S.C. 371(c)(2)).
   a. ☐ is attached hereto.
   b. ☐ has been previously submitted under 35 U.S.C. 154(d)(4).
7. ☐ Amendments to the claims of the International Application under PCT Article 19 (35 U.S.C. 371 (c)(3))
   a. ☐ are attached hereto (required only if not communicated by the International Bureau).
   b. ☐ have been communicated by the International Bureau.
   c. ☐ have not been made; however, the time limit for making such amendments has NOT expired.
   d. ☐ have not been made and will not be made.
8. ☐ An English language translation of the amendments to the claims under PCT Article 19 (35 U.S.C. 371(c)(3)).
9. ☒ An oath or declaration of the inventor(s) (35 U.S.C. 371 (c)(4)).
10. ☐ An English language translation of the annexes of the International Preliminary Examination Report under PCT Article 36 (35 U.S.C. 371 (c)(5)).
11. ☒ A copy of the International Preliminary Examination Report (PCT/IPEA/409).
12. ☒ A copy of the International Search Report (PCT/ISA/210).

Items 13 to 20 below concern document(s) or information included:

13. ☒ An Information Disclosure Statement under 37 CFR 1.97 and 1.98.
14. ☐ An assignment document for recording. A separate cover sheet in compliance with 37 CFR 3.28 and 3.31 is included.
15. ☒ A **FIRST** preliminary amendment.
16. ☐ A **SECOND** or **SUBSEQUENT** preliminary amendment.
17. ☐ A substitute specification.
18. ☐ A change of power of attorney and/or address letter.
19. ☐ A computer-readable form of the sequence listing in accordance with PCT Rule 13ter.2 and 35 U.S.C. 1.821 - 1.825.
20. ☐ A second copy of the published international application under 35 U.S.C. 154(d)(4).
21. ☐ A second copy of the English language translation of the international application under 35 U.S.C. 154(d)(4).
22. ☒ Certificate of Mailing by Express Mail
23. ☒ Other items or information:

copy of the International Application as published by the International Bureau
duplicate copy of this transmittal letter for charging purposes
return postcard

U.S. APPLICATION NO. (IF KNOWN, SEE 37 CFR	INTERNATIONAL APPLICATION NO.	ATTORNEY'S DOCKET NUMBER
To be assigned 09/830147	PCT/GB99/03488	NIDN-10484

24. The following fees are submitted:.

BASIC NATIONAL FEE (37 CFR 1.492 (a) (1) - (5)) :

		CALCULATIONS PTO USE ONLY
☐	Neither international preliminary examination fee (37 CFR 1.482) nor international search fee (37 CFR 1.445(a)(2)) paid to USPTO and International Search Report not prepared by the EPO or JPO	**$1000.00**
☒	International preliminary examination fee (37 CFR 1.482) not paid to USPTO but International Search Report prepared by the EPO or JPO	**$860.00**
☐	International preliminary examination fee (37 CFR 1.482) not paid to USPTO but international search fee (37 CFR 1.445(a)(2)) paid to USPTO	**$710.00**
☐	International preliminary examination fee (37 CFR 1.482) paid to USPTO but all claims did not satisfy provisions of PCT Article 33(1)-(4)	**$690.00**
☐	International preliminary examination fee (37 CFR 1.482) paid to USPTO and all claims satisfied provisions of PCT Article 33(1)-(4)	**$100.00**
	ENTER APPROPRIATE BASIC FEE AMOUNT =	**$860.00**
	Surcharge of **$130.00** for furnishing the oath or declaration later than ☐ 20 ☐ 30 months from the earliest claimed priority date (37 CFR 1.492 (e)).	**$0.00**

CLAIMS	NUMBER FILED	NUMBER EXTRA	RATE	
Total claims	16 - 20 =	0	x $18.00	**$0.00**
Independent claims	2 - 3 =	0	x $80.00	**$0.00**
Multiple Dependent Claims **(check if applicable)**.			☐	**$0.00**
	TOTAL OF ABOVE CALCULATIONS =			**$860.00**
☐	Applicant claims small entity status. (See 37 CFR 1.27). The fees indicated above are reduced by 1/2.			**$0.00**
	SUBTOTAL =			**$860.00**
	Processing fee of **$130.00** for furnishing the English translation later than ☐ 20 ☐ 30 months from the earliest claimed priority date (37 CFR 1.492 (f)). +			**$0.00**
	TOTAL NATIONAL FEE =			**$860.00**
☐	Fee for recording the enclosed assignment (37 CFR 1.21(h)). The assignment must be accompanied by an appropriate cover sheet (37 CFR 3.28, 3.31) **(check if applicable).**			**$0.00**
	TOTAL FEES ENCLOSED =			**$860.00**
			Amount to be: refunded	$
			charged	$

a. ☐ A check in the amount of _____ to cover the above fees is enclosed.

b. ☒ Please charge my Deposit Account No. **500-588** in the amount of **$860.00** to cover the above fees. A duplicate copy of this sheet is enclosed.

c. ☒ The Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account No. **500-588** A duplicate copy of this sheet is enclosed.

d. ☐ Fees are to be charged to a credit card. **WARNING:** Information on this form may become public. **Credit card information should not be included on this form.** Provide credit card information and authorization on PTO-2038.

NOTE: Where an appropriate time limit under 37 CFR 1.494 or 1.495 has not been met, a petition to revive (37 CFR 1.137(a) or (b)) must be filed and granted to restore the application to pending status.

SEND ALL CORRESPONDENCE TO:

Royal N. Ronning, Jr.
Amersham Pharmacia Biotech, Inc.
800 Centennial Avenue
Piscataway, New Jersey 08855

(732) 457-8423

SIGNATURE

Royal N. Ronning, Jr.
NAME

32,529
REGISTRATION NUMBER

April 20, 2001
DATE

NIDN-10484

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Application of:	K. Kellar	Group Art Unit:	To be assigned
Serial Number:	To be assigned	Examiner:	To be assigned
Filing Date:	April 20, 2001		
Title:	Europium Switch		

FIRST PRELIMINARY AMENDMENT

Honorable Assistant Commissioner of Patents
Box New Patent Application
Washington, D.C. 20231

Sir:

Please consider the following amendments and remarks in connection with the prosecution of the captioned application, which is a filing under 35 U.S.C. § 371 and claims priority to international application number PCT/GB99/03488 filed October 22, 1999, which is a Continuation-in-Part of United States provisional application number 60/107,212 filed November 5, 1998, and Great Britain application number 9823175.6 filed October 22, 1998.

IN THE CLAIMS

[Claims:]

What is Claimed is:

Please delete claims 5, 7, 8, 9, 21 and 22, without prejudice.

Please amend claim 1 as follows:

1. (amended) A method of generating a contrast enhanced image of a human or non-human animal subject which comprises administering to said subject an effective amount of a magnetic resonance imaging contrast agent and generating an image of at least part of said subject containing said agent, wherein said agent comprises a physiologically tolerable [lanthanide]Europium compound, preferably a chelate complex of Europium or a physiologically tolerable salt thereof having first and second oxidation states which [differ]differs in relaxivity by a factor of at least 5, and wherein said Europium compound is activated by switching between the II and III oxidation states of metal ions *in vivo* whereby contrast difference is enhanced in a body region in which conversion between the oxidation states occurs.[which is convertible *in vivo* from said first to said second oxidation state whereby contrast is enhanced in a body region in which conversion to said second state does or does not occur.]

Please amend claim 2 as follows:

2. (amended) A method as claimed in claim 1 wherein said agent comprises a physiologically tolerable [lanthanide]Europium compound or salt thereof having first and second oxidation states which differ in relaxivity by a factor of at least 10.

Please amend claim 3 as follows:

3. (amended) A method as claimed in claim 1 wherein said agent comprises a physiologically tolerable [lanthanide]Europium compound or salt thereof having first and second oxidation states which differ in relaxivity by a factor of at least 20.

Please amend claim 4 as follows:

4. (amended) A method as claimed in claim 1 wherein said agent comprises a physiologically tolerable [lanthanide]Europium compound or salt thereof having first and second oxidation states which differ in relaxivity by a factor of at least 100.

Please amend claim 6 as follows:

6. (amended) A method as claimed in claim [5]1 wherein said change between two paramagnetic states is effected as a change from a spherically symmetric electronic ground state to a non-spherically symmetric excited state.[non-spherically symmetric electronic ground state to a spherically symmetric electronic ground state, or a change from a non-spherically symmetric electronic ground state to a spherically symmetric excited state.]

Please amend claim 10 as follows:

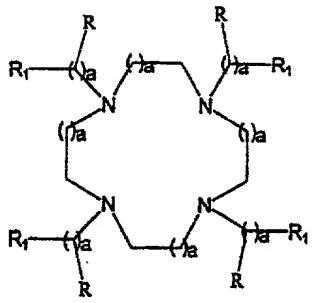
10. (amended) A method as claimed in [any one of claims 7 to 9]claim 1 wherein said chelate complex is a complex of a chelant selected from the group consisting of DTPA, EDTA, DTPA-BMA, DO3A, DOTA, HP-DO3A, TMT and DPDP.

Please amend claim 11 as follows:

11. (amended) A method as claimed in [any one of claims 7 to 9]claim 1 wherein said chelate complex is a complex of a chelant selected from the group consisting of porphyrins and porphyrin-like molecules, phthalocyanines, crown ethers, hemin, heme, chelants having a square planar symmetry, cryptands and cryptates.

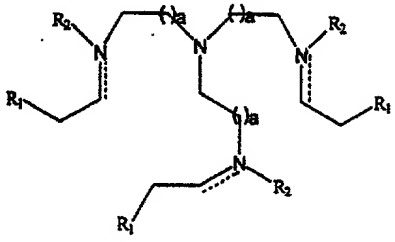
Please amend claim 12 as follows:

12. (amended) A method as claimed in [any one of claims 7 to 9]claim 1 wherein said chelate complex is a complex of a chelant selected from compounds of formulae (I), (II), (III), (IV), (V) and (VI):



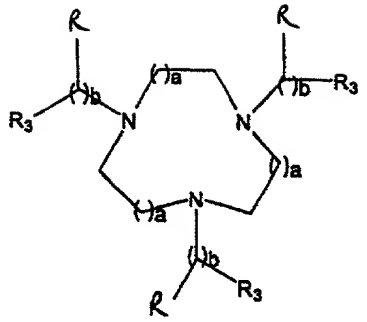
(I)

where each a independently represents an integer between 1 and 3, each R independently represents hydrogen or hydroxy and each R_1 independently represents a carboxylate, phosphate, thioacid, thiol, amino alkoxide or hydroxy group;



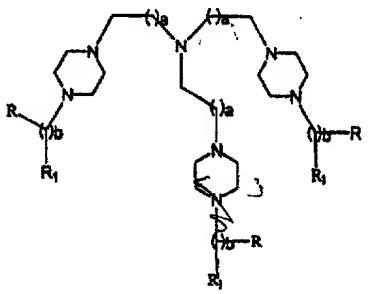
(II)

where a and R_1 are as hereinbefore defined and each R_2 independently represents hydrogen, C_{1-6} alkyl or aryl, with the proviso that R_2 is absent when the double bond is present on the same nitrogen;



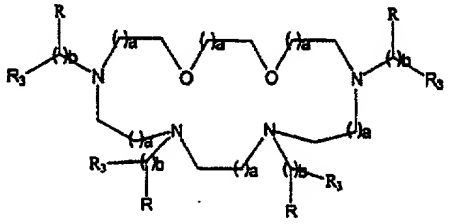
(III)

where a, R and R_2 are as hereinbefore defined, b is an integer between 0-3 and each R_3 independently represents R_1, $NR\text{-}NR_2\text{-}COO^{\theta}$, or $N{=}N\text{-}COO^{\theta}$ when b is positive or each R_3 independently represents $N{=}CH\text{-}COO^{\theta}$ or $NR_2\text{-}CH_2\text{-}COO^{\theta}$;



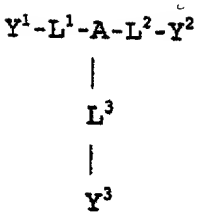
(IV)

where a, b, R and R_1 are as hereinbefore defined;



(V)

where a, b, R and R_3 are as hereinbefore defined;



(VI)

where A is N, CR_4, P, P=O, *cis,cis,cis*-1,3,5-trisubstituted-cyclohexane or an N,N',N"-trisubstituted-triaza 9 to 14 membered macrocyclic ring;

L^1,L^2,L^3 are linker groups which are independently chosen from C_{1-4} alkylene, C_{4-8} cycloalkylene or C_{4-8} o-arylene;

Y^1,Y^2,Y^3 are independently chosen from $-NH_2$, -B(=O)OZ, -N=CR_5-B(=O)OZ, -NR_5-CR_6-B(=O)OZ,-N[CR_6-B(=O)Q]$_2$ and –O-CR_6-B(=O)OZ where B is C or PR_6, each Q is independently –OZ or –NR_6, and Z is H or a counter-ion;

each R_4 and R_5 group is independently chosen from H, C_{1-5} alkyl, C_{1-5} lkoxyalkyl, C_{1-5} hydroxyalkyl, C_{1-5} aminoalkyl, C_{5-10} aryl or C_{1-6} fluoroalkyl;

R_6 is OH, C_{1-6} alkyl, C_{1-6} alkoxyalkyl, C_{1-6} fluoroalkyl, C_{1-10} alkoxy or C_{5-10} aryl;

with the proviso that at least one of Y^1, Y^2 and Y^3 is –N=CR_5-B(=O)OZ.

Please amend claim 13 as follows:

13. (amended) A method as claimed in [any preceding claim]claim 1 wherein said agent is conjugated to a biological vector capable of targeting said agent to a desired region of the body.

Please amend claim 15 as follows:

15. (amended) A method as claimed in [any preceding claim]claim 1 wherein conversion between said first and second oxidation states is effected *in vivo* by a localised normal or abnormal biological process, by an administered chemical agent or by illumination of said agent with light.

Please amend claim 19 as follows:

19. (amended) An MR contrast agent composition comprising as an MR contrast agent a physiologically tolerable [lanthanide]Europium compound, preferably a chelate complex of Europium or a physiologically tolerable[or] salt thereof having first and second oxidation states which [differ]differs in relaxivity by a factor of at least 5, and wherein said Europium compound is activated by switching between the II and III oxidation states of the metal ions *in vivo*[which is convertible *in vivo* from said first to said second oxidation state] whereby contrast difference is enhanced in a body region in which conversion [to said second state does or does not occur]between the oxidation states occurs, together with an optionally encapsulated physiologically tolerable trigger substance capable of converting said contrast agent between said first and second oxidation states.

REMARKS

Claims 1-22 are pending in the instant application. Applicants have deleted claims 5, 7, 8, 9, 21, and 22 and have amended claims 1, 2, 3, 4, 6, 10, 11, 12, 13, 15, and 19 to more fully conform with U.S. practice and to delete multiple dependencies. A copy of the marked up claims showing the amendments, as well as a clean copy of the claims encompassing the amendments, is attached hereto.

Applicants respectfully assert that all amendments are fairly based on the specification, and respectfully request their entry.

Applicants believe that the claims, as amended, are in allowable form, and earnestly solicit the allowance of claims 1-20.

Respectfully submitted,

Royal N. Ronning, Jr. 32,529
Attorney for Applicants

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P. O. Box 1327
Piscataway, New Jersey 08855-1327

Tel: (732) 457-8423
Fax: (732) 457-8463

Amended Claims (marked up copy showing amendment(s))

[Claims:]

What is Claimed is:

1. (amended) A method of generating a contrast enhanced image of a human or non-human animal subject which comprises administering to said subject an effective amount of a magnetic resonance imaging contrast agent and generating an image of at least part of said subject containing said agent, wherein said agent comprises a physiologically tolerable [lanthanide]Europium compound, preferably a chelate complex of Europium or a physiologically tolerable salt thereof having first and second oxidation states which [differ]differs in relaxivity by a factor of at least 5, and wherein said Europium compound is activated by switching between the II and III oxidation states of metal ions *in vivo* whereby contrast difference is enhanced in a body region in which conversion between the oxidation states occurs.[which is convertible *in vivo* from said first to said second oxidation state whereby contrast is enhanced in a body region in which conversion to said second state does or does not occur.]

2. (amended) A method as claimed in claim 1 wherein said agent comprises a physiologically tolerable [lanthanide]Europium compound or salt thereof having first and second oxidation states which differ in relaxivity by a factor of at least 10.

3. (amended) A method as claimed in claim 1 wherein said agent comprises a physiologically tolerable [lanthanide]Europium compound or salt thereof having first and second oxidation states which differ in relaxivity by a factor of at least 20.

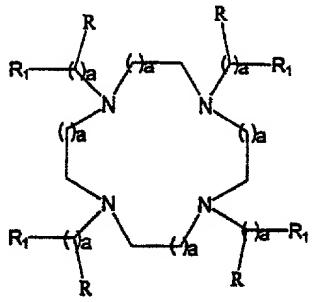
4. (amended) A method as claimed in claim 1 wherein said agent comprises a physiologically tolerable [lanthanide]Europium compound or salt thereof having first and second oxidation states which differ in relaxivity by a factor of at least 100.

6. (amended) A method as claimed in claim [5]1 wherein said change between two paramagnetic states is effected as a change from a spherically symmetric electronic ground state to a non-spherically symmetric excited state.[non-spherically symmetric electronic ground state to a spherically symmetric electronic ground state, or a change from a non-spherically symmetric electronic ground state to a spherically symmetric excited state.]

10. (amended) A method as claimed in [any one of claims 7 to 9]claim 1 wherein said chelate complex is a complex of a chelant selected from the group consisting of DTPA, EDTA, DTPA-BMA, DO3A, DOTA, HP-DO3A, TMT and DPDP.

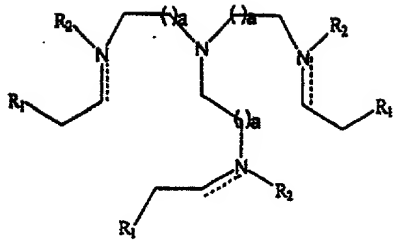
11. (amended) A method as claimed in [any one of claims 7 to 9]claim 1 wherein said chelate complex is a complex of a chelant selected from the group consisting of porphyrins and porphyrin-like molecules, phthalocyanines, crown ethers, hemin, heme, chelants having a square planar symmetry, cryptands and cryptates.

12. (amended) A method as claimed in [any one of claims 7 to 9]claim 1 wherein said chelate complex is a complex of a chelant selected from compounds of formulae (I), (II), (III), (IV), (V) and (VI):



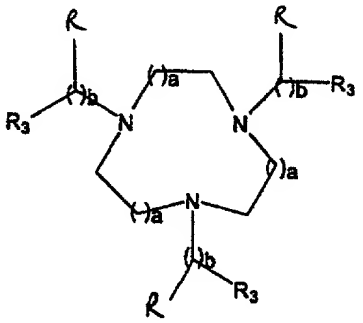
(I)

where each a independently represents an integer between 1 and 3, each R independently represents hydrogen or hydroxy and each R_1 independently represents a carboxylate, phosphate, thioacid, thiol, amino alkoxide or hydroxy group;



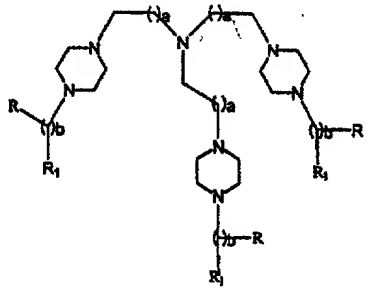
(II)

where a and R_1 are as hereinbefore defined and each R_2 independently represents hydrogen, C_{1-6} alkyl or aryl, with the proviso that R_2 is absent when the double bond is present on the same nitrogen;



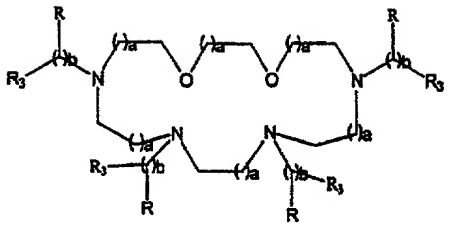
(III)

where a, R and R_2 are as hereinbefore defined, b is an integer between 0-3 and each R_3 independently represents R_1, $NR\text{-}NR_2\text{-}COO^{\theta}$, or $N{=}N\text{-}COO^{\theta}$ when b is positive or each R_3 independently represents $N{=}CH\text{-}COO^{\theta}$ or $NR_2\text{-}CH_2\text{-}COO^{\theta}$;



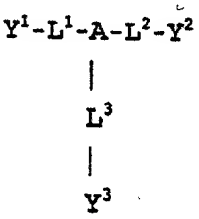
(IV)

where a, b, R and R_1 are as hereinbefore defined;



(V)

where a, b, R and R_3 are as hereinbefore defined;



(VI)

where A is N, CR_4, P, P=O, *cis,cis,cis*-1,3,5-trisubstituted-cyclohexane or an N,N',N"-trisubstituted-triaza 9 to 14 membered macrocyclic ring;

L^1,L^2,L^3 are linker groups which are independently chosen from C_{1-4} alkylene, C_{4-8} cycloalkylene or C_{4-8} o-arylene;

Y^1,Y^2,Y^3 are independently chosen from $-NH_2$, -B(=O)OZ, $-N=CR_5$-B(=O)OZ, $-NR_5$-CR_6-B(=O)OZ,-N[CR_6-B(=O)Q]$_2$ and –O-CR_6-B(=O)OZ where B is C or PR_6, each Q is independently –OZ or $-NR_6$, and Z is H or a counter-ion;

each R_4 and R_5 group is independently chosen from H, C_{1-5} alkyl, C_{1-5} lkoxyalkyl, C_{1-5} hydroxyalkyl, C_{1-5} aminoalkyl, C_{5-10} aryl or C_{1-6} fluoroalkyl;

R_6 is OH, C_{1-6} alkyl, C_{1-6} alkoxyalkyl, C_{1-6} fluoroalkyl, C_{1-10} alkoxy or C_{5-10} aryl;

with the proviso that at least one of Y^1, Y^2 and Y^3 is $-N=CR_5$-B(=O)OZ.

13. (amended) A method as claimed in [any preceding claim]claim 1 wherein said agent is conjugated to a biological vector capable of targeting said agent to a desired region of the body.

15. (amended) A method as claimed in [any preceding claim]claim 1 wherein conversion between said first and second oxidation states is effected *in vivo* by a localised

normal or abnormal biological process, by an administered chemical agent or by illumination of said agent with light.

19. (amended) An MR contrast agent composition comprising as an MR contrast agent a physiologically tolerable [lanthanide]Europium compound, preferably a chelate complex of Europium or a physiologically tolerable[or] salt thereof having first and second oxidation states which [differ]differs in relaxivity by a factor of at least 5, and wherein said Europium compound is activated by switching between the II and III oxidation states of the metal ions *in vivo*[which is convertible *in vivo* from said first to said second oxidation state] whereby contrast difference is enhanced in a body region in which conversion [to said second state does or does not occur]between the oxidation states occurs, together with an optionally encapsulated physiologically tolerable trigger substance capable of converting said contrast agent between said first and second oxidation states.

Claims (encompassing any amendments)

What is Claimed is:

1. (amended) A method of generating a contrast enhanced image of a human or non-human animal subject which comprises administering to said subject an effective amount of a magnetic resonance imaging contrast agent and generating an image of at least part of said subject containing said agent, wherein said agent comprises a physiologically tolerable Europium compound, preferably a chelate complex of Europium or a physiologically tolerable salt thereof having first and second oxidation states which differs in relaxivity by a factor of at least 5, and wherein said Europium compound is activated by switching between the II and III oxidation states of metal ions *in vivo* whereby contrast difference is enhanced in a body region in which conversion between the oxidation states occurs.

2. (amended) A method as claimed in claim 1 wherein said agent comprises a physiologically tolerable Europium compound or salt thereof having first and second oxidation states which differ in relaxivity by a factor of at least 10.

3. (amended) A method as claimed in claim 1 wherein said agent comprises a physiologically tolerable Europium compound or salt thereof having first and second oxidation states which differ in relaxivity by a factor of at least 20.

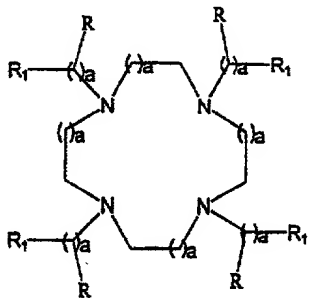
4. (amended) A method as claimed in claim 1 wherein said agent comprises a physiologically tolerable Europium compound or salt thereof having first and second oxidation states which differ in relaxivity by a factor of at least 100.

6. (amended) A method as claimed in claim 1 wherein said change between two paramagnetic states is effected as a change from a spherically symmetric electronic ground state to a non-spherically symmetric excited state.

10. (amended) A method as claimed in claim 1 wherein said chelate complex is a complex of a chelant selected from the group consisting of DTPA, EDTA, DTPA-BMA, DO3A, DOTA, HP-DO3A, TMT and DPDP.

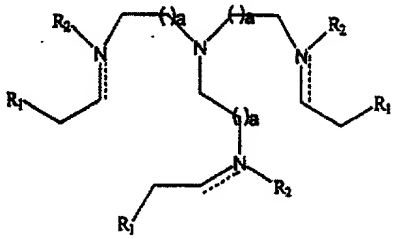
11. (amended) A method as claimed in claim 1 wherein said chelate complex is a complex of a chelant selected from the group consisting of porphyrins and porphyrin-like molecules, phthalocyanines, crown ethers, hemin, heme, chelants having a square planar symmetry, cryptands and cryptates.

12. (amended) A method as claimed in claim 1 wherein said chelate complex is a complex of a chelant selected from compounds of formulae (I), (II), (III), (IV), (V) and (VI):



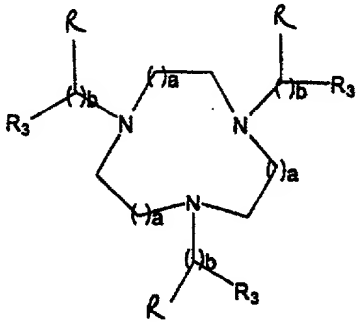
(I)

where each a independently represents an integer between 1 and 3, each R independently represents hydrogen or hydroxy and each R_1 independently represents a carboxylate, phosphate, thioacid, thiol, amino alkoxide or hydroxy group;



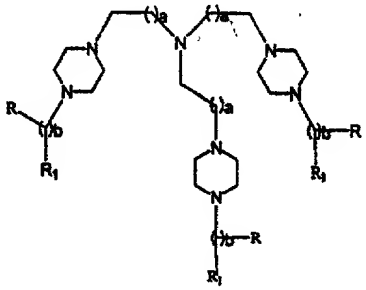
(II)

where a and R_1 are as hereinbefore defined and each R_2 independently represents hydrogen, C_{1-6} alkyl or aryl, with the proviso that R_2 is absent when the double bond is present on the same nitrogen;



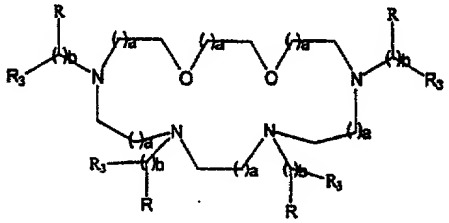
(III)

where a, R and R_2 are as hereinbefore defined, b is an integer between 0-3 and each R_3 independently represents R_1, $NR\text{-}NR_2\text{-}COO^{\theta}$, or $N{=}N\text{-}COO^{\theta}$ when b is positive or each R_3 independently represents $N{=}CH\text{-}COO^{\theta}$ or $NR_2\text{-}CH_2\text{-}COO^{\theta}$;



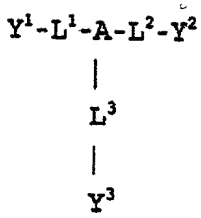
(IV)

where a, b, R and R_1 are as hereinbefore defined;



(V)

where a, b, R and R_3 are as hereinbefore defined;



(VI)

where A is N, CR_4, P, P=O, *cis,cis,cis*-1,3,5-trisubstituted-cyclohexane or an N,N',N"-trisubstituted-triaza 9 to 14 membered macrocyclic ring;

L^1,L^2,L^3 are linker groups which are independently chosen from C_{1-4} alkylene, C_{4-8} cycloalkylene or C_{4-8} o-arylene;

Y^1,Y^2,Y^3 are independently chosen from $-NH_2$, -B(=O)OZ, $-N=CR_5-B(=O)OZ$, $-NR_5-CR_6-B(=O)OZ$,$-N[CR_6-B(=O)Q]_2$ and $-O-CR_6-B(=O)OZ$ where B is C or PR_6, each Q is independently –OZ or $-NR_6$, and Z is H or a counter-ion;

each R_4 and R_5 group is independently chosen from H, C_{1-5} alkyl, C_{1-5} lkoxyalkyl, C_{1-5} hydroxyalkyl, C_{1-5} aminoalkyl, C_{5-10} aryl or C_{1-6} fluoroalkyl;

R_6 is OH, C_{1-6} alkyl, C_{1-6} alkoxyalkyl, C_{1-6} fluoroalkyl, C_{1-10} alkoxy or C_{5-10} aryl;

with the proviso that at least one of Y^1, Y^2 and Y^3 is $-N=CR_5-B(=O)OZ$.

13. (amended) A method as claimed in claim 1 wherein said agent is conjugated to a biological vector capable of targeting said agent to a desired region of the body.

14. A method as claimed in claim 13 wherein said biological vector is selected from the group consisting of an antibody, and antibody fragment and an oligopeptide binding motif.

15. (amended) A method as claimed in claim 1 wherein conversion between said first and second oxidation states is effected *in vivo* by a localised normal or abnormal biological process, by an administered chemical agent or by illumination of said agent with light.

16. A method as claimed in claim 15 wherein conversion between said first and second oxidation states is effected *in vivo* by the presence or absence of oxygen or of oxidation or reduction promoting agents, from a change in temperature or as a result of an increase or decrease in pH at the target site, or as a result of the presence of a specific enzyme.

17. A method as claimed in claim 15 wherein said chemical agent is a redox reagent capable of delivery to or accumulation at a desired target site within the body.

18. A method as claimed in claim 15 wherein conversion between said first and second oxidation states is effected by application of light having a wavelength of from 600 to 1300 nm.

19. (amended) An MR contrast agent composition comprising as an MR contrast agent a physiologically tolerable Europium compound, preferably a chelate complex of Europium or a physiologically tolerable salt thereof having first and second oxidation states which differs in relaxivity by a factor of at least 5, and wherein said Europium compound is activated by switching between the II and III oxidation states of the metal ions *in vivo* whereby contrast difference is enhanced in a body region in which conversion between the oxidation states occurs, together with an optionally encapsulated physiologically tolerable trigger substance capable of converting said contrast agent between said first and second oxidation states.

20. A composition as claimed in claim 19 wherein said trigger substance is an enzyme, a redox agent or a free radical scavenger.

Compound

This invention relates to compounds useful as contrast agents in magnetic resonance imaging and to methods of imaging using such compounds.

Magnetic resonance (MR) imaging is a well established imaging modality in which the image is derived from the intensity of the nmr signal from protons (usually water protons) in the subject under study. Because most tissue has an approximately 80% water content, contrast in MR imaging is attained by the application of pulse sequences that reveal differences in the relaxation times (T_1 and T_2) of the tissues. As with other diagnostic imaging modalities such as CT and ultrasound, contrast agents may be used in MR imaging procedures to enhance contrast in the images produced, e.g. to allow clearer differentiation between different tissue types or between healthy and non-healthy tissue. In MR imaging, the contrast agents conventionally are chelated paramagnetic species (e.g. Gd DTPA, Gd.DTPA-BMA and Gd HP-DO3A, available commercially under the trade names Magnevist, Omniscan and Pro-Hance), which achieve contrast enhancement because of their relaxivities, their ability to decrease the relaxation times of water protons.

A proposal has been made, in WO96/38184, that "triggered" paramagnetic metal ion complexes be used as MR contrast agents. As described in WO96/38184, the trigger mechanism has the paramagnetic complex being "turned on" as an MR contrast agent by the presence of a target substance which interacts with the agent complexing the paramagnetic metal ion so as to free an inner sphere coordination site and allow water molecule exchange to take place at the freed-up site. In the absence of the target substance, the complexed paramagnetic metal ion has no inner sphere coordination

sites available for water molecule exchange and in this state the contrast agent is considered to be turned off.

This concept of a triggered MR contrast agent however has a major defect which will hinder practical application of the concept. Thus in the "turned off" state the complex will still function fairly effectively as an MR contrast agent since both inner-sphere and outer-sphere water coordination contributes to the agent's relaxivity. The inventors of WO96/38184 indirectly acknowledge this drawback when they refer to the degree of change in MR signal that is sufficient to be detectable in the image as being as low as 2 to 5%, well below the conventionally accepted threshold of 10% (see for example Chem. Rev. 87: 901-927 (1987)). The relaxivity of the gadolinium chelates of WO96/38184 will be reduced by about one half (but not eliminated) if inner sphere coordination of water is prevented. Thus the triggered agents of WO96/38184 are not so much switched off as dimmed by about half by the absence of the target substance. Accordingly the selectivity and sensitivity desired by the authors is not possible due to the unavoidable outer-sphere contribution.

It has since been proposed by the applicants in WO98/47539 that triggered MR imaging of contrast agents may be achieved significantly more efficiently by using the "target substance" to change the contrast agent between states in which the relaxivity (r_1) differs by a factor of at least 5. This is achieved either by switching to a lower relaxivity state with little or no relaxivity or alternatively by switching on/off an inner sphere deriving relaxivity which is significantly higher than (e.g. 5 times or greater than) the outer sphere deriving component of the relaxivity.

Certain contrast agents which have now been found to be particularly suitable for use in "triggered" MR imaging techniques are those comprising lanthanide compounds which can be switched between first and second

oxidation states differing in relaxivity by a factor of 5 or more, preferably 10 or more, but can be much higher, e.g. at least 20, at least 100 or even significantly larger if the relaxivity of the low relaxivity state approaches zero. "Triggered" MR imaging is achieved using such agents as a result of a redox reaction.

Thus viewed from one aspect the invention provides a method of generating a contrast enhanced image of a human or non-human (preferably mammalian) animal subject which comprises administering to said subject an effective amount of a magnetic resonance imaging contrast agent and generating an image of at least part of said subject containing said agent, wherein said agent comprises a physiologically tolerable lanthanide compound or salt thereof having first and second oxidation states which differ in relaxivity by a factor of at least 5, preferably at least 10, but can be much higher, e.g. at least 20, at least 100 or even significantly larger if the relaxivity of the low relaxivity state approaches zero, and which is convertible *in vivo* from said first to said second oxidation state whereby contrast is enhanced in a body region in which conversion to said second state does or does not occur.

In the method of the invention the change between high and low relaxivity states is effected as a change in the oxidation state of the lanthanide metal in the contrast agent between higher and lower relaxivity states. In this regard, the means for effecting the change between higher and lower relaxivity states may be localised normal or abnormal biological activity, an administered chemical agent or an applied physical means (e.g. illumination with light).

The change in oxidation state may give rise to a change in relaxivity in a number of ways, e.g. as a result of a change from a paramagnetic to a diamagnetic

state, from a diamagnetic to a paramagnetic state, or from one paramagnetic state to another. Conveniently, the change in relaxivity of the contrast agent is effected as a change from one paramagnetic state to another, e.g. from a non-spherically symmetric electronic ground state to a spherically symmetric electronic ground state, or a change from a non-spherically symmetric electronic ground state to a spherically symmetric excited state. The non-spherically symmetric state will have a much lower associated relaxivity than the spherically symmetric state and accordingly the contrast difference between the "on" and "off" states of the switchable agent is large.

Preferably, the contrast agent for use in the method of the invention is a chelate complex of a lanthanide metal ion in which the chelated metal ion is capable of redox conversion from one oxidation state to another (one or both of which are paramagnetic). On/off switching by a redox reaction may occur either as a result of oxidation or reduction of the chelated metal ion. Depending on the particular lanthanide metal present, its initial oxidation state and the nature of the complexing agent, this may bring about either a decrease or increase in relaxivity of the contrast agent.

Preferred contrast agents for use in the invention are those in which the "on position" corresponds to a state in which the relaxivity is as high as possible and in which the "off position" corresponds to a state in which the relaxivity is as low as possible, preferably close to zero. In this regard, contrast agents comprising Europium compounds, in particular chelate complexes of Europium, which are activated by switching between the II and III oxidation states, e.g. by biological activity or by redox reagents are particularly preferred for use in the method of the

invention.

Due to a half filled 4f shell, Eu(II) complexes have a spherically-symmetric electronic ground state ($^8S_{7/2}$) and therefore have long electron spin relaxation times and particularly high relaxivities. Eu(III) complexes, on the other hand, have a $^7F_0$ electronic ground state and very short electronic relaxation times Eu(III) is only paramagnetic because excited states must be considered, but these states are not spherically symmetric. Consequently, electronic relaxation times are very short and relaxivities are essentially zero. Oxidation of Eu(II) to Eu(III) thus causes a substantial loss of relaxivity which is readily detectable as a marked change in MR signal intensity. The transition from Eu(II) to Eu(III) thus provides a highly sensitive "on-off" switch. Moreover, the transition from Eu(II) to Eu(III) is particularly sensitive to oxygen concentration and pH:

$$Eu(II) + H^+ + \tfrac{1}{4}O_2 = Eu(III) + \tfrac{1}{2}H_2O \quad (I)$$

$$Eu(II) + H^+ = Eu(III) + \tfrac{1}{2}H_2 \quad (II)$$

Equation (I) is dominant when oxygen is present.

Suitable complexing agents for use in the invention are those which present the lanthanide metal, in particular Europium, in a biotolerable form, e.g. a polyaminopolyacid chelating agent of the type well known for MR agents and radiopharmaceuticals, for example DTPA, EDTA, DTPA-BMA, DO3A, DOTA, HP-DO3A, TMT, DPDP, etc. In this regard the reader is referred to the patent publications of metal chelates from Schering, Nycomed, Salutar, Bracco, Mallinckrodt, Guerbet, Sterling Winthrop, etc. Examples include US-A-4647447, US-A-5362475, US-A-5534241, US-A-5358704, US-A-5198208, US-A-4963344, EP-A-230893, EP-A-130934, EP-A-606683, EP-A-438206, EP-A-434345, WO 97/00087, WO 96/40274, WO 96/30377, WO 96/28420, WO 96/16678, WO 96/11023,

WO 95/32741, WO 95/27705, WO 95/26754, WO 95/28967, WO 95/28392, WO 95/24225, WO 95/17920, WO 95/15319, WO 95/09848, WO 94/27644, WO 94/22368, WO 94/08624, WO 93/16375, WO 93/06868, WO 92/11232, WO 92/09884, WO 92/08707, WO 91/15467, WO 91/10669, WO 91/10645, WO 91/07191, WO 91/05762, WO 90/12050, WO 90/03804, WO 89/00052, WO 89/00557, WO 88/01178, WO 86/02841 and WO 86/02005.

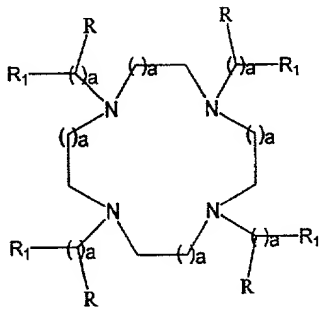
Thus appropriate complexing agents include macrocyclic chelants having an open coordination site for water, e.g. porphyrin-like molecules and the pentaaza macrocyclic ligands of Zhang et al (Inorg. Chem. 37(5):956-963, 1998), phthalocyanines, crown ethers e.g. nitrogen crown ethers such as the sepulchrates, cryptates etc., hemin (protoporphyrin IX chloride) and heme (available from Porphyrin Products, Inc. of Logan, Utah, USA) and chelants having a square-planar symmetry. Alternatively, the complexing agent may comprise a polyacid ligand capable of protonating a coordinating group thereby freeing up a coordination site for water molecules at a particular pH.

Other complexing agents of use according to the invention include polyoxadiazamacrobicyclic ligands ("cryptands") known to form stable coordination compounds ("cryptates") with several lanthanide metal ions, in particular with Europium (see J. Am Chem. Soc. 102(7): 2278-2285, 1980). In this regard, the (2.2.1), (2.2.2) and (2_β.2.1) cryptands are particularly suitable for use in the invention [the numerals within the parentheses refer to the number of oxygen atoms in the polyether bridges joining the nitrogen bridgeheads in the bicyclic molecule. Thus, (2.2.1) cryptand = 4,7,13,16,21-pentaoxa-1,10-diazabicyclo[8.8.5]tricosane and (2.2.2) cryptand = 4,7,13,16,21,24-hexaoxa-1,10-diazabicyclo [8.8.8]hexacosane. The ligand (2_β.2.1) is similar to (2.2.1) except that one of the central dioxyethylene groups is replaced by the analogous

catechol].

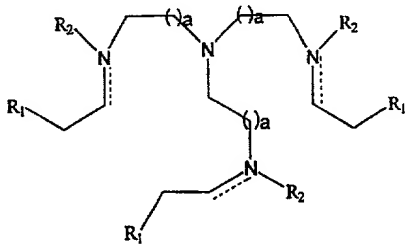
Particular Europium compounds for use in the invention include the following cryptates: $Eu^{II}(2.2.1)$, $Eu^{II}(2_\beta.2.1)$, $Eu^{II}(2.2.2)$ and the corresponding Eu^{III} complexes, $Eu^{III}(2.2.1)$, $Eu^{III}(2_\beta.2.1)$ and $Eu^{III}(2.2.2)$.

Suitable complexing agents also include ligands of formula (I)



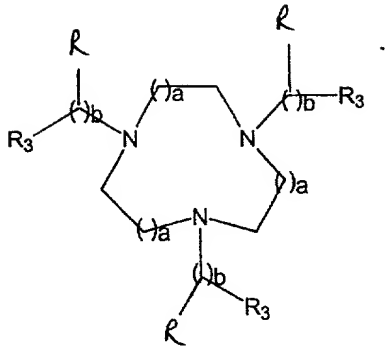
where each a independently represents an integer between 1 and 3, preferably 1, each R independently represents hydrogen or hydroxy and each R_1 independently represents a carboxylate, phosphate, thioacid, thiol, amino alkoxide or hydroxy group, preferably carboxylate;

formula (II)



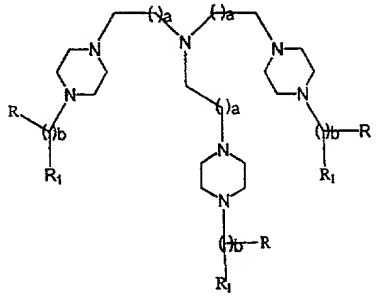
where a and R_1 are as hereinbefore defined and each R_2 independently represents hydrogen, C_{1-6} alkyl, e.g. methyl or isopropyl, aryl, e.g. phenyl, with the proviso that R_2 is absent when the double bond is present on the same nitrogen;

formula (III)

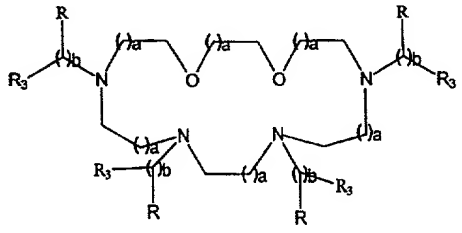


where a, R and R_2 are as hereinbefore defined, b is an integer between 0-3 and each R_3 independently represents R_1, $NR-NR_2-COO^{\ominus}$, or $N=N-COO^{\ominus}$ when b is positive or each R_3 independently represents $N=CH-COO^{\ominus}$ or $NR_2-CH_2-COO^{\ominus}$;

formula (IV)

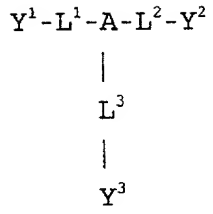


where a, b, R and R_1 are as hereinbefore defined; and formula (V)



where a, b, R and R_3 are as hereinbefore defined.

Also of use are complexing agents of formula (VI)



where A is N, CR_4, P, P=O, *cis,cis,cis*-1,3,5-trisubstituted-cyclohexane or an N,N',N"-trisubstituted-triaza 9 to 14 membered macrocyclic ring;

L^1,L^2,L^3 are linker groups which are independently chosen from C_{1-4} alkylene, C_{4-8} cycloalkylene or C_{4-8} o-arylene;

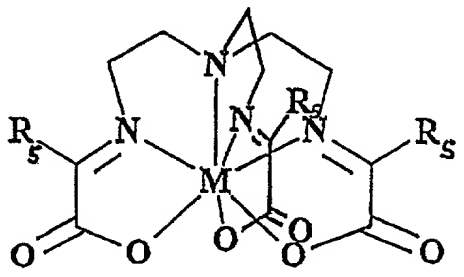
Y^1,Y^2,Y^3 are independently chosen from $-NH_2$, $-B(=O)OZ$, $-N=CR_5-B(=O)OZ$, $-NR_5-CR_6-B(=O)OZ$, $-N[CR_6-B(=O)Q]_2$ and $-O-CR_6-B(=O)OZ$ where B is C or PR_6, each Q is independently -OZ or $-NR_6$, and Z is H or a counter-ion;

each R_4 and R_5 group is independently chosen from H, C_{1-5} alkyl, C_{1-5} alkoxyalkyl, C_{1-5} hydroxyalkyl, C_{1-5} aminoalkyl, C_{5-10} aryl or C_{1-6} fluoroalkyl;

R_6 is OH, C_{1-6} alkyl, C_{1-6} alkoxyalkyl, C_{1-6} fluoroalkyl, C_{1-10} alkoxy or C_{5-10} aryl;

with the proviso that at least one of Y^1, Y^2 and Y^3 is $-N=CR_5-B(=O)OZ$.

For example



Specific complexing agents of use according to the invention include

Claims:

1. A method of generating a contrast enhanced image of a human or non-human animal subject which comprises administering to said subject an effective amount of a magnetic resonance imaging contrast agent and generating an image of at least part of said subject containing said agent, wherein said agent comprises a physiologically tolerable lanthanide compound or salt thereof having first and second oxidation states which differ in relaxivity by a factor of at least 5, and which is convertible *in vivo* from said first to said second oxidation state whereby contrast is enhanced in a body region in which conversion to said second state does or does not occur.

2. A method as claimed in claim 1 wherein said agent comprises a physiologically tolerable lanthanide compound or salt thereof having first and second oxidation states which differ in relaxivity by a factor of at least 10.

3. A method as claimed in claim 1 wherein said agent comprises a physiologically tolerable lanthanide compound or salt thereof having first and second oxidation states which differ in relaxivity by a factor of at least 20.

4. A method as claimed in claim 1 wherein said agent comprises a physiologically tolerable lanthanide compound or salt thereof having first and second oxidation states which differ in relaxivity by a factor of at least 100.

5. A method as claimed in any one of claims 1 to 4 wherein the change between said first and said second oxidation states is effected as a change from a

paramagnetic to a diamagnetic state, as a change from a diamagnetic to a paramagnetic state, or as a change between two paramagnetic states of the lanthanide metal ion.

6. A method as claimed in claim 5 wherein said change between two paramagnetic states is effected as a change from a non-spherically symmetric electronic ground state to a spherically symmetric electronic ground state, or a change from a non-spherically symmetric electronic ground state to a spherically symmetric excited state.

7. A method as claimed in any preceding claim wherein said agent is a chelate complex of a lanthanide metal ion, or a physiologically tolerable salt thereof.

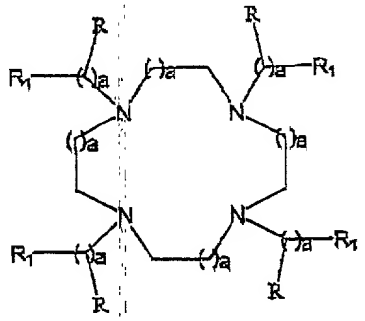
8. A method as claimed in any preceding claim wherein said agent is a Europium compound, preferably a chelate complex of Europium or a physiologically tolerable salt thereof.

9. A method as claimed in claim 8 wherein said Europium compound is activated by switching between the II and III oxidation states of the metal ion.

10. A method as claimed in any one of claims 7 to 9 wherein said chelate complex is a complex of a chelant selected from the group consisting of DTPA, EDTA, DTPA-BMA, DO3A, DOTA, HP-DO3A, TMT and DPDP.

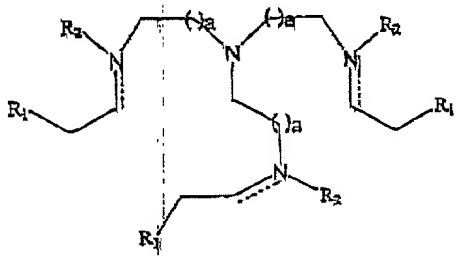
11. A method as claimed in any one of claims 7 to 9 wherein said chelate complex is a complex of a chelant selected from the group consisting of porphyrins and porphyrin-like molecules, phthalocyanines, crown ethers, hemin, heme, chelants having a square planar symmetry, cryptands and cryptates.

12. A method as claimed in any one of claims 7 to 9 wherein said chelate complex is a complex of a chelant selected from compounds of formulae (I), (II), (III), (IV), (V) and (VI):



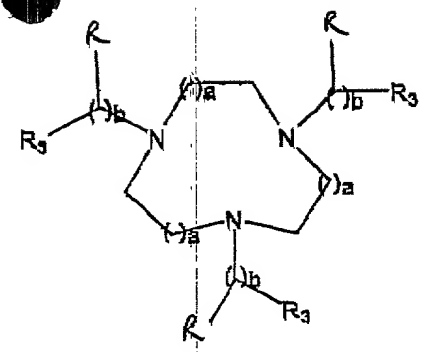
(I)

where each a independently represents an integer between 1 and 3, each R independently represents hydrogen or hydroxy and each R_1 independently represents a carboxylate, phosphate, thioacid, thiol, amino alkoxide or hydroxy group;



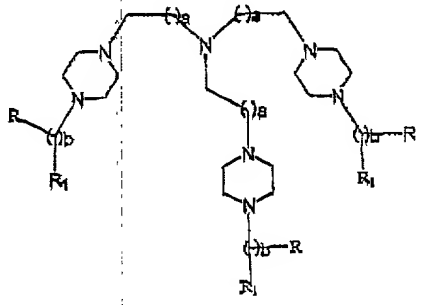
(II)

where a and R_1 are as hereinbefore defined and each R_2 independently represents hydrogen, C_{1-6} alkyl or aryl, with the proviso that R_2 is absent when the double bond is present on the same nitrogen;



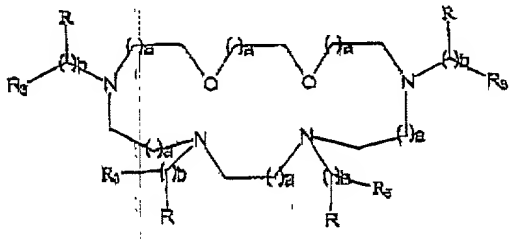
(III)

where a, R and R_2 are as hereinbefore defined, b is an integer between 0-3 and each R_3 independently represents R_1, $NR-NR_2-COO^{\ominus}$, or $N=N-COO^{\ominus}$ when b is positive or each R_3 independently represents $N=CH-COO^{\ominus}$ or $NR_2-CH_2-COO^{\ominus}$;



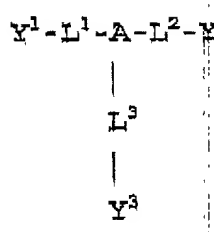
(IV)

where a, b, R and R_1 are as hereinbefore defined;



(V)

where a, b, R and R_3 are as hereinbefore defined;



(VI)

where A is N, CR_4, P, P=O, *cis,cis,cis*-1,3,5-trisubstituted-cyclohexane or an N,N',N''-trisubstituted-triaza 9 to 14 membered macrocyclic ring;

L^1,L^2,L^3 are linker groups which are independently chosen from C_{1-4} alkylene, C_{4-8} cycloalkylene or C_{4-8} o-arylene;

Y^1,Y^2,Y^3 are independently chosen from $-NH_2$, $-B(=O)OZ$, $-N=CR_5-B(=O)OZ$, $-NR_5-CR_6-B(=O)OZ$, $-N[CR_6-B(=O)Q]_2$ and $-O-CR_6-B(=O)OZ$ where B is C or PR_6, each Q is independently $-OZ$ or $-NR_6$, and Z is H or a counter-ion;

each R_4 and R_5 group is independently chosen from H, C_{1-5} alkyl, C_{1-5} alkoxyalkyl, C_{1-5} hydroxyalkyl, C_{1-5} aminoalkyl, C_{5-10} aryl or C_{1-6} fluoroalkyl;

R_6 is OH, C_{1-6} alkyl, C_{1-6} alkoxyalkyl, C_{1-6} fluoroalkyl, C_{1-10} alkoxy or C_{5-10} aryl;

with the proviso that at least one of Y^1, Y^2 and Y^3 is $-N=CR_5-B(=O)OZ$.

13. A method as claimed in any preceding claim wherein said agent is conjugated to a biological vector capable of targeting said agent to a desired region of the body.

14. A method as claimed in claim 13 wherein said biological vector is selected from the group consisting of an antibody, an antibody fragment and an oligopeptide binding motif.

15. A method as claimed in any preceding claim wherein conversion between said first and second oxidation states is effected *in vivo* by a localised normal or

abnormal biological process, by an administered chemical agent or by illumination of said agent with light.

16. A method as claimed in claim 15 wherein conversion between said first and second oxidation states is effected *in vivo* by the presence or absence of oxygen or of oxidation or reduction promoting agents, from a change in temperature or as a result of an increase or decrease in pH at the target site, or as a result of the presence of a specific enzyme.

17. A method as claimed in claim 15 wherein said chemical agent is a redox reagent capable of delivery to or accumulation at a desired target site within the body.

18. A method as claimed in claim 15 wherein conversion between said first and second oxidation states is effected by application of light having a wavelength of from 600 to 1300 nm.

19. An MR contrast agent composition comprising as an MR contrast agent a physiologically tolerable lanthanide compound or salt thereof having first and second oxidation states which differ in relaxivity by a factor of at least 5, and which is convertible *in vivo* from said first to said second oxidation state whereby contrast is enhanced in a body region in which conversion to said second state does or does not occur, together with an optionally encapsulated physiologically tolerable trigger substance capable of converting said contrast agent between said first and second oxidation states.

20. A composition as claimed in claim 19 wherein said trigger substance is an enzyme, a redox agent or a free radical scavenger.

21. The use of a physiologically tolerable MR contrast agent substance comprising a physiologically tolerable lanthanide compound or salt thereof having first and second oxidation states which differ in relaxivity by a factor of at least 5, and which is convertible *in vivo* from said first to said second state whereby contrast is enhanced in a body region in which conversion to said second state does or does not occur, for the manufacture of a diagnostic contrast medium for use in a method of diagnosis involving image generation according to a method as claimed in any one of claims 1 to 18.

22. Use as claimed in claim 21 for the manufacture of a diagnostic contrast medium for use in a method of detecting malignant melanoma, squamous cell carcinoma, sarcomas or adenocarcinomas.

6-11-01

PCT B

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DECLARATION FOR UTILITY OR DESIGN PATENT APPLICATION (37 CFR 1.63)

☐ Declaration Submitted with Initial Filing OR ☒ Declaration Submitted after Initial Filing (surcharge (37 CFR 1.16 (e)) required)

Attorney Docket Number	NIDN-10484
First Named Inventor	Kellar
COMPLETE IF KNOWN	
Application Number	09 / 830,147
Filing Date	20-Apr-2001
Group Art Unit	To be assigned
Examiner Name	To be assigned

As a below named inventor, I hereby declare that:

My residence, post office address, and citizenship are as stated below next to my name.

I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled.

Europium Switch

(Title of the Invention)

the specification of which
☐ is attached hereto
OR
☒ was filed on (MM/DD/YYYY) 04/20/2001 as United States Application Number or PCT International Application Number 09/830,147 and was amended on (MM/DD/YYYY) _____ (if applicable)

I hereby state that I have reviewed and understand the contents of the above identified specification, including the claims, as amended by any amendment specifically referred to above.

I acknowledge the duty to disclose information which is material to patentability as defined in 37 CFR 1.56.

I hereby claim foreign priority benefits under 35 U.S.C 119(a)-(d) or 365(b) of any foreign application(s) for patent or inventor's certificate, or 365(a) of any PCT international application which designated at least one country other than the United States of America, listed below and have also identified below, by checking the box, any foreign application for patent or inventor's certificate, or of any PCT international application having a filing date before that of the application on which priority is claimed.

Prior Foreign Application Number(s)	Country	Foreign Filing Date (MM/DD/YYYY)	Priority Not Claimed	Certified Copy Attached? YES	NO
9823175.6	GB	10/22/1998	☐	☐	☒
			☐	☐	☐
			☐	☐	☐
			☐	☐	☐

☐ Additional foreign application numbers are listed on a supplemental priority data sheet PTO/SB/02B attached hereto.

I hereby claim the benefit under 35 U.S.C. 119(e) of any United States provisional application(s) listed below.

Application Number(s)	Filing Date (MM/DD/YYYY)	
60/107,212	11/05/1998	☐ Additional provisional application numbers are listed on a supplemental priority data sheet PTO/SB/02B attached hereto.

Burden Hour Statement. This form is estimated to take 0.4 hours to complete. Time will vary depending upon the needs of the individual case. Any comments on the amount of time you are required to complete this form should be sent to the Chief Information Officer, Patent and Trademark Office, Washington, DC 20231. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Assistant Commissioner for Patents, Washington, DC 20231

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DECLARATION — Utility or Design Patent Application

I hereby claim the benefit under 35 U.S.C. 120 of any United States application(s), or 365(c) of any PCT international application designating the United States of America, listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States or PCT International application in the manner provided by the first paragraph of 35 U.S.C. 112, I acknowledge the duty to disclose information which is material to patentability as defined in 37 CFR 1.56 which became available between the filing date of the prior application and the national or PCT international filing date of this application

U.S. Parent Application or PCT Parent Number	Parent Filing Date (MM/DD/YYYY)	Parent Patent Number (if applicable)
PCT/GB99/03488, which is a CIP of 60/107,212 filed 11/05/1998	10/22/1999	

☐ Additional U.S or PCT international application numbers are listed on a supplemental priority data sheet PTO/SB/03

As a named inventor, I hereby appoint the following registered practitioner(s) to prosecute this application and to transact all business in the Patent and Trademark Office connected therewith: ☒ Customer Number 22840 OR ☐ Registered practitioner(s) name/registration number listed below

Place Customer Number Bar Code Label here

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Name	Registration Number	Name	Registration Number

☐ Additional registered practitioner(s) named on supplemental Registered Practitioner Information sheet PTO/SB/02C attached hereto

Direct all correspondence to: ☒ Customer Number or Bar Code Label 22840 OR ☐ Correspondence address below

Name					
Address					
Address					
City		State		ZIP	
Country		Telephone		Fax	

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true, and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under 18 U.S.C. 1001 and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Name of Sole or First Inventor: ☐ A petition has been filed for this unsigned inventor

Given Name (first and middle [if any])	Family Name or Surname
Kenneth	Kellar

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City		State		ZIP		Country	

☐ Additional inventors are being named on the ____ supplemental Additional Inventor(s) sheet(s) PTO/SB/02A attached hereto